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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/930,915
Filing Date: August 15, 2001
Appellant(s): BIRKETT, ASHLEY J.

Gamson
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed February 26, 2010, appealing from the Office action mailed March 4, 2009.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner.

The rejection of Claims 12-14, 17, 27-29, 36, 37, 59-62 and 76 under 35 USC 103(a), as being unpatentable over Pumpens *et al*. (1995), in view of Zlotnick *et al* (1997), as applied to Claims 1-9, 15, 16, 18-26, 30-33, 35, 38, 42-58, 63-75, 77 and 78, further in view of Birkett (US 6,231,864, cited in IDS), is withdrawn in view of Appellant's argument. Appellant states that Birkett (US 6,231,864), constitutes prior art under 102(e), is not "by another". In view of the statement, the rejection is withdrawn.

The rejection of Claims 1-9, 12-33, 35-38 and 42-78 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 98-109 of 10/805,913; and Claims 79-115 of 10/806,006 is moot in view of the abandon of the applications.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

- Metzger, K. et al. "Proline-138 is essential for the assembly of hepatitis B virus core protein" J. Gen. Virology, 79:587-590, 1998.
- Pumpens et al. "Hepatitis B virus core particles as epitope carriers" Intervirology 38:63-74, 1995.
- Zlotnick A. et al. "Localization of the C terminus of the assembly domain of hepatitis B virus capsid protein: Implications for morphogenesis and organization of encapsidated RNA" 94:9556-9561, 1997.
- Thornton et al. US Pat. 5,143,726

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections – 35 USC § 112-Scope of enablement

I. Claims 1-9, 12-33, 35-38 and 42-78 are rejected under 35 USC 112, first paragraph, because the specification, while being enabling for an HBc chimer of SEQ ID NOs: 246-251, does not reasonably provide enablement for an HBc chimer containing up to about 5% substituted amino acid residues in the HBc SEQ ID NOs: 246-251. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In making a determination as to whether an application has met the requirements for enablement under 35 USC 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered. In the present case, the factors that are considered most relevant are the presence or absence of working examples, the direction or guidance presented, and the nature of the invention.

1. Claims 1-9, 12-33, 35-38 and 42-78 read on a chimeric hepatitis B core (HBc) protein comprising heterologous epitope peptide, wherein the HBc has up to about 5 percent substituted

amino acid residues in amino acids 1-149 of native HBc sequences SEQ ID Nos: 246-251, and wherein the HBc chimer is self-assembling into particles that are substantially free of binding to nucleic acids and have enhanced stability.

2. Since there is no structural limitation to up to "about 5 percent substituted amino acid residues in the sequence of amino acids 1-149 of SEQ ID Nos: 246-251(native HBc sequences) from position 1 through 149", the scope of the claims encompasses a large number of HBc chimers comprising up to about 5% unspecified mutations variously arranged along the amino acids 1-149 of a native HBc, but having enhanced particle stability. However, while the specification has disclosed that a chimer molecule comprising native human HBc, such as SEQ ID NO:247 (e.g. in Examples 22 and 23), it has not disclosed any chimers comprising alternative HBc variants, which can have up to 5 percent random mutations in HBc sequences of SEQ ID Nos: 246-251, and can still form particles, like native HBc, and have enhanced particle stability. The specification has also failed to provide the necessary guidance that would lead one to such genus of particles that are made of alternative HBc variants and have enhanced stability.

3. The prior art teaches that it is highly uncertain which changes in amino acids 1-149 of native HBc would lead to a chimer with enhanced stability. Even a single substitution can have an unpredictable effect on the assembly of HBc particles. For example, Metzger teaches that a single amino acid change, Pro-138 to Gly, prevents the HBc protein self-assembling into particles (Metzger, J. Gen. Virology, 79:587-590, 1998). Thus, the art teaches that there is no correlation between the stability of HBc particles and an arbitrary percentage of random change of amino acids along positions 1-149 of HBc. A single amino acid substitution in amino acids 1 to 149 of native HBc, as shown by Metzger, can create problems resulting from changes in the

conformation of HBc particle that can't be adequately predicted in advance.

4. In view of the empirical and unpredictable nature of the invention with regard to a chimer comprising HBc variants with enhanced stability, and lack of guidance and working examples in the specification, those skilled in the art would not be able to make the claimed HBc chimers that both contain up to about 5% substituted amino acid residues in native HBc, and having enhanced stability. The specification does not enable one of ordinary skill in the art to make the invention commensurate in scope with these claims.

Claim Rejections – 35 USC § 112-Written Description

II. Claims 1-9, 12-33, 35-38 and 42-78 are rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was made in the Office action dated March 4, 2009, and is re-irritated herein for convenience.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 USC 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli

Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

It is also noted that even the presence of multiple species within a claimed genus does not necessarily demonstrate possession of the genus. See, In re Smyth, 178 U.S.P.Q. 279 at 284-85 (CCPA 1973) (stating "**where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated**, one skilled in the art may be found not to have been placed in possession of a genus or combination claimed at a later date in the prosecution of a patent application."); and University of California v. Eli Lilly and Co., 43 USPQ2d 1398, at 1405 (Fed Cir 1997)(citing Smyth for support). Thus, when a claim covers a genus of inventions, the specification must provide sufficient written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a sufficient number of examples so that one skilled in the art would recognize from the specification the scope of what is being claimed, or provided a function and a structure correlating with that function. Moreover, in situations where the operability of species other than those provided is uncertain, additional support is required over that which would be required where greater certainty is present.

5. The scope of the claims encompasses a large number of HBc chimers that contain a 5% substitution frequency in SEQ ID Nos: 246-251 (183 amino acids). Furthermore, the claims require that the specified HBc particle has enhanced stability comparing to native HBc. In support of the claims, the specification shows a few species of HBc chimer (for example, 7 of 24 chimers in Example 14) were able to yield particles, see Table 13, Example 14. Of the modified

HBc chimers in the above example, however, 14 of the 24 tested lost their ability to form particles. Thus, the specification shows that it is uncertain if HBc chimers containing a 5% substitution frequency in SEQ ID Nos: 246-251 can form viral-like particles as can HBc, or would the resultant HBc particles have enhanced stability as claimed (Also see discussion in Para 35 and 36 below)

6. The art indicates that the result of peptide modification is, in general, unpredictable. Modification of a peptide by as little as one amino acid can cause a change in conformation, and thus peptide function, that can't be predicted in advance. Metzger teaches that a single amino acid change, Pro-138 to Gly, prevents self-assembly of the HBc protein into particles (Metzger, J. Gen. Virology, 79:587-590, 1998). Thus, substitution of a single amino acid can have an unpredictable effect on the assembly of HBc particles. These teachings in the art are consistent with the result shown in the specification Example 14.

7. Although the specification discloses a few species of HBc chimers made of native HBc, the specification has not disclosed any HBc chimer particles made of alternative HBc variants that contain up to 5% mutation in amino acids 1-149 of native HBc. The specification has failed to provide an adequate description which amino acid mutations in native HBc can still form viral-like particles, and has enhanced stability when compared to native HBc. Given that the scope of the claims encompasses a large number of modified HBc chimers, and considering the unpredictable particle stability of the majority of HBc chimers, the specification has not disclosed sufficient species of HBc chimers that have enhanced stability to support the broadly claimed genus. Consequently, the skilled artisan would reasonably conclude Applicant was not in possession of the claimed HBc chimers that have both 5% substitution of amino acid residues

in the HBc SEQ ID NOs: 246-251, and enhanced stability.

Claim Rejections - 35 USC § 103

III. Claims 1-9, 15, 16, 18-26, 30-33, 35, 38, 42-58, 63-75, 77 and 78 are rejected under 35 USC 103(a), as being unpatentable over Pumpens *et al.* (1995) in view of Zlotnick *et al* (1997). This rejection was made in the Office action dated July 26, 2004; and maintained for the reason set forth in the Office actions dated May 9, 2005; July 10, 2006; February 23, 2007; October 29, 2007; August 4, 2008; and March 4, 2009. The rejection is re-iterated herein for convenience.

8. The claims are directed to a recombinant chimer hepatitis B core (HBc) protein molecule up to about 515 amino acid residues in length that (a) contains an HBC sequence of at least about 130 of the *N*-terminal 150 amino acid residues of the HBc molecule that includes a peptide-bonded heterologous epitope, contains one to ten cysteine residues toward the *C*-terminus of the molecule from the *C*-terminal residue of the HBc sequence and within about 30 residues from the *C*-terminus of the chimer molecule [*C*-terminal cysteine residue(s)], contains a sequence of at least 5 amino acid residues from HBC position 135 to the HBC *C*-terminus, said chimer molecules containing no more than 5 percent substituted amino acid residues in the HBc sequence, self-assembling into particles that are substantially free of binding to nucleic acids on expression in a host cell, and said particles being more stable than are particles formed from an otherwise identical HBC chimer that lacks said C-terminal cysteine residue(s) or in which a C-terminal cysteine residue present in the chimer molecule is replaced by another residue.

9. Pumpens teaches native HBc (183 amino acids) can self-assemble into particles comprising a variety of HBc units, see left col. p. 64. Both full-length HBc (1-183 amino acids) and *C*-terminal truncated HBc (HBcΔ; 1-149 amino acids) have been used as foreign peptide (like epitope) carriers, wherein the foreign peptide is inserted in the *N*-terminal, immunodominant loop and the *C*-terminus of HBc; see e.g. Summary, Fig. 1, Tables 1-3. These recombinant HBc chimers contain an HBC sequence of at least about 130 of the *N*-terminal 150 amino acid residues of the HBc molecule.

10. The combination above meets the limitations as found in Claims 1, 2, 9, 15, 16, 18, 24, 32, 33, 36-38, 42, 45, 51-58, 63-66, 68-71, 75 and 78. Additionally, Pumpens further describes elements of HBc chimers that are found as limitations in the dependent claims. For instance, Pumpens teaches heterologous epitopes inserts as outlined above. This is relevant to Claims 2, 12, 13, 15 and 16. See also table 2, on page 67, for linker residues at the internal insertion site. As to Claims 3, 43 and 67, Pumpens teaches that the heterologous epitope can be a B-cell epitope. (See page 71, col. 1) As to Claims 4, 8, 25, 26, 29, 35, 48, 49 and 50, Pumpens teaches that heterologous epitopes can be peptide bonded to the *N*-terminal region (page 70, col. 1) or the other regions. These can be B-cell epitopes or T-cell epitopes. (See page 71, col. 2, final paragraph). Pumpens teaches the internal insertion site, frequently referred to as the immunodominant loop. This is relevant to Claims 5, 6, 70 and 71, among others. As to Claims 19-23, 69, and 72-74, Pumpens teaches that HBc can contain multiple heterologous epitopes (See page 71, col. 1, second full paragraph). As to Claims 28, 30-31, 44, 45, 65 and 68, Pumpens teaches that HBc chimers can handle a wide range of insert sizes. Pumpens teaches sizes including ones as small as 7 residues. As to Claim 47, Table 1 (page 66) of Pumpens *et al* (1995)

indicates that HBc has been used to display epitopes from HIV.

11. Pumpens makes two critical points on page 67 regarding to HBcΔ chimers. First, Pumpens discloses that HBcΔ chimers are capable of self-assembly, and do not bind or 'pack' nucleic acid. (page 67, col. 1). Pumpens reports the problem that "capsids formed by *C*-terminally truncated HBc monomers are less stable than the corresponding full-length protein particles."

12. However, Pumpens does not teach that adding a *C*-terminal cysteine residue to HBcΔ to provide a stabilizing effect.

13. ZIotnick *et al*. (1997) teach adding a *C*-terminal cysteine residue to HBcΔ provides a stabilizing effect. (See e.g. pp. 9556 and 9558; and Fig. 2). Zlotnick made two HBc variants, Cp*149, which contain 1-149 amino acids of native HBc but the Cys 48, Cys 61 and Cys 107 of native HBcΔ have each been substituted by Alanine; and Cp*150, which has same sequence as Cp*149, but has an additional C-terminal cysteine residue at residue 150, see Fig. 1a. Zlotnick show that Cp*150 can polymerized and form particles, which were found to be more stable in SDS electrophoresis and size exclusion chromatography; see e.g. Para 1 and 2, left col. p. 9558; and Fig. 2.

14. Zlotnick also teaches that, unlike full-length HBc, Cp183, HBcΔ particles, both Cp149 and Cp*150, are substantially free of binding to nucleic acids upon expression in host cells; See e.g. description of Fig.3; and Para 2, and Fig. 4, right col. p. 9560. Zlotnick's HBcΔ Cp*150 contains the HBc sequence from position 135-149 with a terminal cysteine at position 150, thus meeting the limitations cited in the claims (e.g. Claim 1b, (i) and (ii)). Zlotnick clearly demonstrates that HBcΔ particles having *C*-terminal cys are more stable than are particles

formed from otherwise identical HBc chimers that lack said *C*-terminal cysteine residue(s). (see page 9558, col. 1, first and second full paragraphs).

15. It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the HBcΔ chimer particles of Pumpens by adding a C-terminal cystine to HBcΔ as taught by Zlotnick in order to make more sable HBcΔ chimer particles. The skilled artisan would have been motivated to do so because it was well known in the art that HBcΔ chimers, while still capable of self-assembly, were less stable than their full-length counterparts, and that by adding back a cystine to *C*-terminal HBcΔ could achieve a more stable chimer as shown by Zlotnick. One of ordinary skill in the art would have expected to achieve a more stable HBcΔ chimer by the addition of a cysteine residue, because Zlotnick teaches that the addition of a cysteine to the *C*-terminus of an HBc molecule with a *C*-terminal truncation results in enhanced stability. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

IV. Claims 12-14, 17, 27-29, 36, 37, 59-62 and 76 are rejected under 35 USC 103(a), as being unpatentable over Pumpens *et al.* (1995) and Zlotnick *et al* (1997) as applied to Claims 1-9, 15, 16, 18-26, 30-33, 35, 38, 42-58, 63-75, 77 and 78, further in view of Thornton *et al.* (US Pat. 5,143,726). This rejection was made in the Office action dated February 23, 2007, and maintained for the reason set forth in the Office actions dated October 29, 2007, August 4, 2008, and March 4, 2009. The rejection is re-iterated herein for convenience.

16. Claims 12-14, 17, 27-29, 36, 37, 59-62 and 76 are directed to an immunogenic HBc

chimer, **wherein said chimer contains a heterologous linker residue for a conjugated epitope**, wherein said heterologous linker residue for a conjugated epitope is peptide-bonded at a position in the HBc sequence between amino acid residues 76 and 85, and at least 4 residues of the HBc sequence of positions 76 through 85 are present, wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said heterologous linker residue for a conjugated epitope, wherein said heterologous linker residue for a conjugated epitope is selected from the group consisting of a **lysine**, aspartic acid, glutamic acid, **cysteine** and a tyrosine residue, wherein said heterologous linker residue for a conjugated epitope or a heterologous epitope is a heterologous epitope, wherein said heterologous epitope comprises up to about 245 amino acid residues, wherein said heterologous epitope is a B cell epitope.

17. The relevance of Pumpens (1995) is set forth *supra*. Briefly, Pumpens teaches immunogenic compositions and vaccines using recombinant HBc chimer molecules up to about 380 or 600 amino acid residues in length. Pumpens teaches that both full-length HBc and *C*-terminal truncated HBcΔ can form capsid particles. The HBc and HBcΔ chimers can carry B-cell and T-cell epitopes at their N-terminal, C-terminal or at internal immunodominant loop sites at positions 76 through 85 (See Figure 1 and Tables 1 through 3). Pumpens also teaches such chimers can contain two epitopes at both the immunodominant loop and the *C*-terminus (see Table 2). Pumpens discloses that HBc chimers with *C*-terminal truncations are capable of self-assembly and do not bind or 'pack' nucleic acids in their capsid particles (page 67, col. 1).

18. The relevance of Zlotnick is set forth *supra* in Para 13 and 14.

19. Thornton teaches the use of HBc as an immunogenic carrier molecule where a polypeptide is linked to the carrier/core molecule through an amino acid side chain on the core

molecule (see abstract, Columns 9 and 10, and Line 5-14, Column 21). Thornton teaches that operatively linking a polypeptide immunogen to HBcAg particles increases the immunogenicity of the linked immunogen to an unexpected degree through the operation of HBcAg's previously unknown T cell-dependent and T cell-independent determinants. Thornton indicates: "Methods for operatively linking individual polypeptides through an amino acid residue side chain to form an immunogenic conjugate, i.e., a branched-chain polypeptide polymer, are well known in the art." (Line 13-45, column 10). Useful side chain functional groups include epsilon-amino groups, beta- or gamma-carboxyl groups, thiol (--SH) groups and aromatic rings (e.g. **tyrosine** and **histidine**). Furthermore, Thornton teaches that, as is well known in the art, both the HBcAg protein and polypeptide immunogen can be used in their native form or their functional group content may be modified by succinylation of **lysine** residues or reaction with **cysteine**-thiolactone. The polypeptides can also be modified to incorporate spacer arms, such as hexamethylenediamine or other bifunctional molecules of similar size, to facilitate linking (Line 13-45, col. 10).

20. One of ordinary skill in the art would have been motivated to combine the teachings of Thornton with that of Pumpens and Zlotnick in order to make a HBcΔ molecule that could present an epitope via a side-chain. One would have been motivated to do so, given the suggestion by Thornton that operatively linking a polypeptide immunogen to HBcAg particles increases the immunogenicity of the polypeptide, and given the teaching by Zlotnick that HBcΔ with additional Cys at its *C*-terminus have greatly enhances the stability and does not pack viral RNA into the particles. There would have been a reasonable expectation of success, given the knowledge that both HBc and HBcΔ have been successfully used for displaying heterologous

epitopes at their *N*-, and *C*-termini, and immunodominant loop at positions 76 through 85, as taught by Pumpens and Thornton, and given the knowledge that methods for operatively linking individual polypeptides through an amino acid residue side chain to form an immunogenic conjugate are well known in the art, as taught by Thornton. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

V. Claims 1-9, 12-33, 35-38 and 42-78 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over (1) Claims 1-46 of copending Application No. 10/732,862. (2) Claims 1-53 of 10/787,734; (3) Claims 98-109 of 10/805,913; (4) Claims 79-115 of 10/806,006, (5) Claims 47-85 of 11/508,655, and (6) Claims 1-22, 25 and 26 of 11/507,083. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed recombinant chimer HBc protein of the instant application are obvious variations of the claimed HBc chimers of the reference claims.

21. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

VI. Claims 1-9, 12-33, 35-38 and 42-78 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-19 of U.S. Patent No. 6,231,864 ('864), in view of Zlotnick (PNAS,1997, 94(18):9556-61)

22. Claims 1-9 of '864 teach a modified hepatitis B core protein comprising a chemically reactive amino acid residue, preferably in an immunodominant region of the nucleocapsid protein. The modified hepatitis B core protein or its aggregated nucleocapsid protein particles can be pendently linked to a hapten to form a modified nucleocapsid conjugate. The modified hepatitis B core protein can also be modified to include a T cell epitope.

23. Zlotnick teaches recombinant *C*-terminal deleted HBc (HBcΔ) molecules that are capable of assembling into capsids and do not pack viral RNA within their capsids. Zlotnick teaches that an addition of Cys at the *C*-terminus of HBcΔ can enhance the stability of HBcΔ (p. 9558).

24. One of ordinary skill in the art would have been motivated to combine the teachings of Birkett with that of Zlotnick in order to make an HBcΔ molecule that could present an epitope *via* a side-chain. One would have been motivated to do so, and would have had a reasonable expectation of success, given the knowledge that both HBc and HBcΔ have been successfully used for displaying heterologous epitopes on HBc particles, as taught by Birkett, and given the knowledge that methods for operatively linking individual haptens to polypeptides through an amino acid residue side chain to form an immunogenic conjugate are well known in the art, as taught by Birkett, see e.g. col. 13 and 14, Therefore, the instant claims would have been *prima facie* obvious over Claims 1-19 of U.S. Patent No. 6,231,864 ('864), in view of Zlotnick.

(10) Response to Argument

I. Claims 1-9, 12-33, 35-38 and 42-78 fail to comply with scope of enablement requirement, because the specification does not reasonably provide enablement for a HBc

chimer containing up to about 5% substituted amino acid residues in the HBc SEQ ID NOs: 246-251.

25. Appellant presents three arguments in traversal of this rejection. First, the Appellant argues that the current claims have a limitation of the *inclusion of a peptide-bonded heterologous epitope or linker residue present in the immunodominant loop,* and a limitation of *containing 1-10 cysteine residues at the C-terminus.* Appellant asserts that these limitations have not been taken into account by the Action. Therefore, at the outset, the Action's arguments do not pertain to the current set of claims (Appeal brief, bridging Para between p. 12 and 13)

26. This argument is not convincing because all limitations of HBc chimer cited in the claims have been considered. The rejection recites: "...because the specification, while being enabling for a HBc chimer of SEQ ID NOs: 246-251, does not reasonably provide enablement for a HBc chimer containing up to about 5% substituted amino acid residues in the HBc SEQ ID NOs: 246-251" see p. 3 above. Here, "an HBc chimer" means a chimeric peptide comprising both native HBc sequence and heterologous sequences, including the limitations of "*a peptide-bonded heterologous epitope or linker residue present in the immunodominant loop"* and *"containing 1-10 cysteine residues at the C-terminus".* Thus, all limitations cited in the claims have been considered when the action addresses enablement for an HBc chimer containing up to about 5% substituted amino acid residues in HBc SEQ ID NOs: 246-251.

27. Moreover, it is noted that Appellant's argument has not specifically addressed how "a limitation of the *inclusion of a peptide-bonded heterologous epitope or linker residue present in the immunodominant loop"* would have supported the enablement of the claimed HBc chimer both containing up to about 5% substituted amino acid residues in a native HBc and having

enhanced stability. In contrast to Appellant's argument, the specification Para [0016] recites:

"Chimeric hepatitis B core particles bearing internal insertions often appear to have a less ordered structure, when analyzed by electron microscopy, compared to particles that lack heterologous epitopes [Schodel *et al.* (1994) J. Exp. Med., 180:1037-1046]. ...In some cases, the insertion of heterologous epitopes into *C*-terminally truncated HBc particles has such a dramatic destabilizing affect that hybrid particles cannot be recovered following heterologous expression [Schodel *et al.* (1994) Infect. Immunol., 62:1669-1676]. Thus, many chimeric HBc particles are so unstable that they fall apart during purification to such an extent that they are unrecoverable or they show very poor stability characteristics, making them problematic for vaccine development."

In view of the specification Para [0016], it appears that instability of HBc chimer particles comprising heterologous epitopes is a problem well known in the art, and insertions of heterologous epitope peptides are uncertain factors that often negatively affect the stability of HBc particles. Thus, Appellant's argument (1) based on the limitation of the *inclusion of a peptide-bonded heterologous epitope* does not support enablement of an HBc chimer both containing up to about 5% substituted amino acid residues in HBc SEQ ID NOs: 246-251 and having enhanced stability.

28. Regarding to the limitation of *"containing 1-10 cysteine residues at the C-terminus",* Appellant has not presented any evidence showing how this limitation would have supported the enablement of the claimed HBc chimer both containing up to about 5% substituted amino acid residues in a native HBc and having enhanced stability. Also see discussion in Para 30 and 31 below. Thus, Appellant's argument (1) is not persuasive.

29. Further, Appellant argues (2) that the specification provides evidence of the chimeric particles having enhanced stabilities. Specifically, Example 22, Fig. 3, shows that HBc chimer

V2.Pf1+C150, which contain an additional cystine at the *C*-terminus of HBc1-149, forms particles more stable than that of V2.Pf1, which lacks an additional cystine at the *C*-terminus of HBc1-149. Similarly, Example 23, Fig. 8, shows HBc chimer V12.Pf1+C150, which contain an additional cystine at the *C*-terminus of HBc1-149, forms particles more stable than that of V12.Pf1, which lacks an additional cystine at the C-terminus of HBc1-149. Appellant argues that these data show the *C*-terminal cysteine-stabilized particles are more stable immediately on production (of the chimer particles), as well as after incubation at 37°C for various time periods. The stabilized particles also exhibit enhanced immunogenicity. (Appeal Brief, pp.13-15)

30. In response, Appellant's argument is not relevant because it's based on the enabled embodiment, which does not support the entire scope of the claims. This rejection is scope of enablement as recited: "Claims 1-9, 12-33, 35-38 and 42-78 are rejected under 35 USC 112, first paragraph, because the specification, while being enabling for a HBc chimer of SEQ ID NOs: 246-251, does not reasonably provide enablement for a HBc chimer containing up to about 5% substituted amino acid residues in the HBc SEQ ID NOs: 246-251". It is noted that both constructs V2.Pf1+C150 and V12.Pf1+C150 comprise an HBc sequence 100% identical to human HBc of SEQ ID NO: 247 from position 1 through 149. (Note: C150 means an additional cystine added to the *C*-terminus of HBc1-149). There are no substituted amino acid residues in the HBc sequence from position 1 through 149 in both particles of V2.Pf1+C150 and V12.Pf1+C150. Thus, Examples 22 and 23 are enabled for a HBc chimer made of native HBc of SEQ ID NO: 247, but do not reasonably provide enablement for a HBc chimer containing up to about 5% unspecified mutations in the HBc SEQ ID NOs: 246-251. The specification has not shown any HBc sequence having up to 5% substituted amino acid residues in the HBc sequence

from position 1 through 149 with enhanced stability.

31. More importantly, the enabled embodiment of the specification, such as chimers disclosed in Examples 22 and 23, does not support the enablement of the full scope of the claims. Neither the art nor the specification has established that there is any correlation between the arbitrary up to 5% percentage of random mutations in amino acids 1-149 HBc sequence and the ability of said HBc variants to form particles with enhanced stability. Native HBc molecules of SEQ ID NOs: 246-251 can self-assemble into particles according to a natural mechanism, but not according to any arbitrary percentage of random mutation rates. The prior art, such as the cited Metzger reference, has shown that it is highly uncertain in assembly of stable HBc particles. Moreover, the specification Para [008]-[0011] also recites the teachings in the prior art showing that small changes in amino acids 1-149 of HBc can abrogate HBc capsid assembly (particle formation), or reduced stability of the particles; see the teachings of Para [0008]-[0011] and cited references therein. The specification Para [0016] indicates that chimeric HBc particles bearing internal insertions often appear to have a less ordered structure, and reduced stability. "[M]any chimeric HBc particles are so unstable that they fall apart during purification to such an extent that they are unrecoverable or they show very poor stability characteristics, making them problematic for vaccine development"; see Para [0016]. Thus, one couple of species of HBc chimer, such as V2.Pf1+C150 and V12.Pf1+C150, disclosed in the specification, are not a representative number of the claimed subgenus of HBc chimers having up to 5% substituted amino acid residues in the HBc sequence from position 1 through 149 and having enhanced stability. Thus, Appellant's argument (2) is not persuasive.

32. Finally, Appellant argues (3) that the specification enables the scope of the claims because specification teaches use of LASERGENE software to assist in determining which amino acid residues can be conservatively changed without a loss of biological activity or the ability to form particles.

33. This argument is not convincing. As indicated above, there is no correlation between the stability of HBc particles and the percentage of random changes of amino acids along positions 1-149 of HBc. While a computer program may help one of ordinary skill in the art to see sequences of HBc variants, it does not provides guidance *which* proposed HBc variants would actually result in the desired enhanced stability of HBc chimers as required by the claims.

34. For the reasons discussed above, the rejection of Claims 1-9, 12-33, 35-38 and 42-78 for lacking scope of enablement is maintained.

II. The specification fails to provide adequate description for the claimed subgenus of HBc chimers, which contain up to about 5% substituted amino acid residues in 1-149 amino acids of native HBc SEQ ID NOs: 246-251, and have enhanced stability.

35. Appellant presents three arguments in traversal of this rejection. First, Applicant argues that the Office action has mis-quoted the teaching of Example 14 and Table 1 of the instant application. Applicant requested that this rejection be withdrawn because the basis for rejection was inadvertently taken from another Action. (Appeal Brief, pp. 17 and 18).

36. Appellant is correct by pointing out that Example 14 and Table 1 cited in the rejection were misquoted from another specification of Appellant's by accident. The cited Example 14 and Table 1 are not from the instant specification, but actually from the specification of

Appellant's co-pending application 10/732,862 (20040146524). The Examiner regrets the oversight. However, 10/732,862 is directed to the same subject matter as the instant application, which are HBc chimers with enhanced stability. Example 14 of 10/732,862 shows that only 7 of 24 tested HBc chimers containing less that 5% amino acid substitutions in SEQ ID Nos: 246-251 were able to yield particles, but 14 of the 24 tested HBc chimer lost their ability to form particles; see Table 13. Thus, the evidence in Appellant's co-pending application 10/732,862 shows that it is uncertain if HBc chimers containing a 5% substitution frequency in SEQ ID Nos: 246-251 can form viral-like particles as can HBc, or would the resultant HBc particles have enhanced stability as claimed.

37. Moreover, the rejection is not only based on the teachings of Example 14 of Appellant's co-pending application 10/732,862, but also the state of the art; See Para 6 above. The Office action indicates that is not predictable in the art *which* amino acid mutations in native HBc would result in enhanced stability. Thus, both the prior art and the specification, as well as Example 14 of Appellant's co-pending application 10/732,862, have show that substitution of a single amino acid can result in an unpredictable effect on the ability to assemble of HBc particles. A couple of species of modified HBc chimers disclosed by the specification do not constitute representative numbers for the claimed genus. Since neither the art not the specification has established that there is any correlation between the percentage of substitutions of amino acids of HBc, and the stability of resulting HBc chimers, one of ordinary skill in the art cannot envision what other HBc variants could result in HBc chimer with enhanced stability.

38. Secondly, Appellant argues that the claims are not directed to randomly substituted

amino acid sequences. The specification points out that the amino acid substitutions are to be up to 5% of the sequence, that the substitutions are to be conservative, that guidance as to proper conservative substitutions can be obtained with LASERGENE software and the like, and that the region of substitution is in the non-helical portion of the molecule, within residues 2-15 or 24-50, to assure particle formation. (Appeal Brief, p. 18)

39. This argument is not convincing. The claims recite: "said chimer molecules (i) containing no more than about 5 percent substituted amino acid residues in the HBc sequence corresponding to a sequence of SEQ ID N0:246-251 from position 1 through 149,..."; see e.g. Claim 1. This limitation is "directed to randomly substituted amino acid sequences", not "conservative substitutions... in the non-helical portion of the molecule, within residues 2-15 or 24-50, to assure particle formation" as Appellant alleged. Regarding the guidance of LASERGENE software, while a computer program may help one of ordinary skill in the art to chose which amino acids could be altered, such general direction is not sufficient to predict if the proposed changes would actually result in a desired enhanced stability of the modified HBc as required by the claims.

40. Finally, Appellant asserts again that the current claims also have a limitation of the *inclusion of a peptide-bonded heterologous epitope or linker residue present in the immunodominant loop,* and a limitation of *containing 1-10 cysteine residues at the C-terminus.* These limitations have not been taken into account by the Action. (Appeal Brief, bridging para between p. 18 and 19).

41. This argument again is not convincing because all the limitations cited in the claimed

HBc chimer have been considered in the Office action. See discussion in Para 32-35 above. Appellant has not specifically addressed how a limitation of the *inclusion of a peptide-bonded heterologous epitope or linker residue present in the immunodominant loop,* and a limitation of *containing 1-10 cysteine residues at the C-terminus* would have provided written description of the subgenus of HBc chimers containing up to about 5% substituted amino acid residues in the HBc SEQ ID NOs: 246-251, and having enhanced stability. Thus, this argument again is found not relevant.

III. Claims 1-9, 15-16, 18-26, 30-33, 35, 38, 42-58, 63-75, 77 and 78 are obvious over the teachings of Pumpens in view of Zlotnick.

42. Appellant presents three arguments in traversal of this rejection. Appellant argues (1) that Pumpens does not teach adding 1-10 *C*-terminal cysteines to stabilize the chimeric molecule. Zlotnick does not teach a conjugated epitope present in the HBc immunodominant loop in conjunction with 1-10 cysteine residues at the *C*-terminus of the particle and that these particles are more stable than chimers without the *C*-terminal cysteine residues. Appellant asserts that the reliance on Fig. 1 of Zlotnick is misplaced. Zlotnick teaches substitution of Cys48, Cys61, Cysl07, and Argl50. The present invention does not require these substitutions. There is no suggestion in Zlotnick to make the present chimers as recited in the claims.

43. Appellant's argument (1) is not persuasive because the combined teaching of Pumpens and Zlotnick teaches all the limitations of the claims. Specifically, Pumpens teaches a conjugated epitope present in the HBc immunodominant loop. Zlotnick teaches *C*-terminal-truncated HBc

(HBcΔ), Cp*150, which contains amino acid substitutions of native Cys48, Cys 61 and Cys107 for Ala48, Ala61 and Ala107, and addition of one Cys at the *C*-terminus of the HBcΔ. Cp*150 can self-assemble into particles that are substantially free of binding to nucleic acids on expression in a host cell (see e.g. description of Fig.3; and Para 2, and Fig. 4, right col. p. 9560) Cp*150 particles are more stable than are particles formed from Cp*149, see e.g. Fig. 1a. These teachings by Zlotnick teach the claim limitations of "...said chimer molecules (i) containing no more than about 5 percent substituted amino acid residues in the HBc sequence as compared to a sequence of SEQ ID NOs: 246-251 from position 1 through 149, (ii) self-assembling into particles that are substantially free of binding to nucleic acids on expression in a host cell, and said particles are more stable than are particles formed from otherwise identical HBc chimer molecules that lack said *C*-terminal cysteine residue(s)..." Thus, the combined teaching of Pumpens and Zlotnick teaches every limitation of the claims argued by Appellant. Appellant's argument that Zlotnick teaches substitution of Cys48, Cys61, Cysl07, and Argl50, has mischaracterized Zlotnick's Fig. 1.

44. Appellant further argues (2) that the Zlotnick manuscript is not valid in support of the premise that *C*-terminal cysteines enhance stability because it lacks proper controls. Specifically, Cp149 (Cp*149) is not a proper control for Cp*150 because the length of Cp*150 is not the same as Cp149. As such, it cannot be reasonably concluded by one of skill in the art that the *C*-terminal cysteine was responsible for the alleged increased stabilization. Therefore conclusions gleaned from it are suspect (Appeal Brief, Para 4, p. 20 to Para 1, p. 24).

45. In response to this argument, Zlotnick's Cp*149 appears to be a proper and logic control

for Cp*150 to examine the effect of the *C*-terminal cysteines of HBc. First, the Zlotnick manuscript is published in a peer-reviewed scientific journal. This fact indicates that one of ordinary skill (Reviewers) in the art has accepted the scientific evidence and conclusions presented in the Zlotnick manuscript. Secondly, the instant specification Para [0009] has cited the Zlotnick reference as a relevant prior art, but has not raised any disbelieves and disagrees with evidence presented by Zlotnick. Finally, in contrast to Appellant's argument (2), ironically, Appellant has used same logic controls as Zlotnick's to prove the stability effect of *C*-terminal cysteines of HBc, see Appeal Brief, Para 3, p.13 to last Para, p.14. For example, Appellant shows in Fig. 3 (Example 6) that HBc chimer V2.Pf1+C150 is more stable than its control particle V2.Pf1, wherein V2.Pf1+C150 has same sequence as V2.Pf1, but contains an additional cystine at the *C*-terminus of HBc. Appellant states: "The data from this study are interpreted to mean that the *C*-terminal cysteine-stabilized particles are more stable..." see Appeal brief, Para 3, p. 14. Here, Appellant's V2.Pf1+C150 does not have same length as that of V2.Pf1. Appellant's comparison of V2.Pf1+C150 vs. V2.Pf1 appears to be analogous to Zlotnick's comparison of Cp*150 vs. Cp*149. Thus, Applicant's argument against Zlotnick contradicts his own logic of the argument presented in Appeal Brief, pp.13-14 with respect to the enablement of the claimed invention. Since Appellant's argument is not supported with evidence, it is not found persuasive.

46. Finally, Appellant argues (3) that because Zlotnick suggests that other forces are at work besides cysteine binding in terms of capsid assembly, one of skill in the art would not conclude that *C*-terminal cysteines are responsible for capsid stabilization, but rather the opposite, that

they are not so important. (Appeal Brief, bridging Para between p. 23 and p. 24)

47. This argument is not persuasive. Just because Zlotnick suggests that other forces are at work besides cysteine binding in terms of capsid assembly, it does not mean that the knowledge that *C*-terminal cysteines responsible for capsid stabilization is not important to one of ordinary skill in the art. Zlotnick explicitly teaches that *C*-terminal cysteines are responsible for capsid stabilization in page 9558, col.1, paragraphs 1 and 2, *Results and Discussion*, as recited below:

"When reduced CP*150 capsids were stored without DTT for 2 days, >90% of the protein oxidized to form disulfide-bonded dimers (Fig. 2 *a*). These bonds stabilize the quaternary structure of the capsid, as attested by the observation that oxidized Cp*150 capsids—unlike CP*149 capsids or reduced Cp*150 capsids—are resistant to dissociation by 3.5 M urea (Fig. 2 *b*). Knowledge of the location of residue 150 (see below) indicates that this disulfide bond links two dimers (Fig. 1 *b*) and is distinct from the intradimeric disulfide observed in Cp proteins with native cysteines (16, 25).

Generally, when Cp proteins are stored in a low ionic strength, high pH buffer they do not polymerize (10). However, when stored in this buffer without DTT, Cp*150 dimers assemble into capsids, as determined by negative stain electron microscopy and analytical ultracentrifugation. A high proportion of the protein in these capsids is disulfide-bonded (Fig. 2 *a*). These data show that disulfide bond formation by Cp*150 can promote capsid assembly. Without disulfide formation, higher-order structures do not accumulate in storage buffer, i.e., the rate for dissociation is greater than the rate of association. Formation of these disulfide bonds stabilizes complexes against dissociation. Thus, under these conditions, Cp polymerization appears to involve an equilibrium between subunits, assembly intermediates, and capsids (36). We also note that, in capsids, the cysteine 150 residues from adjacent subunits must be close enough to one another to form a covalent bond, a distance of 4.6–7.4 Å between α carbons (37)". (Underline emphasis added by the examiner)

48. In view of the teachings recited above, one skilled in the art would conclude that Zlotnick explicitly teaches that Cp*150, which contains a *C*-terminal cysteine, plays a critical role for its particle assembly and stability. These facts would lead one skilled in the art to conclude that *C*-terminal cysteines are important for HBc capsid formation and stability.

49. For the reasons discussed above, Appellant's arguments are not sufficient to overcome

the 103 rejection. The rejection is therefore maintained.

IV. Claims 12-14, 17, 27-29, 36, 37, 59-62, and 76 are obvious over Pumpens *et al.*, Zlotnick *et al.*, and Thorton *et al.*

50. Applicant argues that Thornton teaches that HBcAg protein operatively linked though an amino acid residue side chain to a polypeptide immunogen. In contrast, the present invention does not utilize an endogenous amino acid side chain for linking. The present invention utilizes a heterologous linker residue (see Claim 12). Therefore, Thornton's teaching is different from that used in the present application.

51. This argument has been considered but found not persuasive. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). According to MPEP 2143.02, "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F2d 1048, 189 USPQ 143 (CCPA 1976." In the recently decided case of *KSR International Co. v. Teleflex Inc.* (82 U.S.P.Q. 2d1385, 2007), the Supreme Court provided a number of bases on which a claimed invention may be found obvious. In particular, "When there is a design need or market pressure to solve a problem and there are a finite number of identified

predictable potential solutions, a person of ordinary skill has good reason to pursue the known potential options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense". In the present case, the instant claims, such as Claim 12, require said HBc chimer contains a heterologous linker residue for a conjugated epitope. Thornton teaches use of chemically modified residue(s) on HBc for a conjugated epitope, see e.g. Abstract, and last Para, right col. bridge to Para 1, col. 15. Since both the modified HBc residue of the prior art and the "heterologous linker residue" of the claimed HBc chimer function as a linker of a conjugated epitope, they are considered as functional equivalents "for a conjugated epitope". There is reasonable expectation of success that a "heterologous linker residue" can link a polypeptide immunogen as well as a modified amino acid residue of HBc of the prior art. Therefore, Applicant's argument is not found persuasive.

52. In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness. The rejection is maintained.

V. Claims 1-9, 12-33, 35-38 and 42-78 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over (1) Claims 1-46 of copending Application No. 10/732,862. (2) Claims 1-53 of 10/787,734; (3) Claims 98-109 of 10/805,913; (4) Claims 79-115 of 10/806,006, (5) Claims 47-85 of 11/508,655, and (6) Claims 1-22, 25 and 26 of 11/507,083.

53. Appellant acknowledges that application No. 10/787,734 has been issued as US Patent

7,361,352. Appellant states that No. 10/787,734 has issued as U.S. Patent Number 7,361,352. In the event that any of the current claims are ultimately allowed, the filing of a terminal disclaimer will be examined in view of the allowed claims and those of the patent. It is believed to be premature to deal with a terminal disclaimer at the present time.

54. The rejection of on the ground of nonstatutory obviousness-type double patenting as being unpatentable over (1) Claims 1-46 of copending Application No. 10/732,862; Claims 1-53 of 10/787,734 (Now US Patent 7,361,352); Claims 47-85 of 11/508,655, and Claims 1-22, 25 and 26 of 11/507,083, is maintained in view of Appellant's statement.

VI. Claims 1-9, 12-33, 35-38 and 42-78 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-19 of U.S. Patent No. 6,231,864 ('864), in view of Zlotnick (PNAS,1997, 94(18):9556-61)

55. Appellant acknowledges the rejection and states: "In the event that any of the current claims are ultimately allowed, the filing of a terminal disclaimer will be examined in view of the allowed claims and those of the patent. It is believed to be premature to deal with a terminal disclaimer at the present time". The rejection is therefore maintained in view of Appellant's statement.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related

Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/BO PENG/

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